Inhibition of Tumor Growth by Anti Matrix Metalloproteinase-9 DNAzyme

Stefan Schweizer
sschwei1@uthsc.edu

Technology Transfer: Health Science Center (Memphis) Office
Our Solution

The Solution

- A novel efficacious and safe DNAzyme based therapeutic agent for glioma, breast cancer and potentially other cancer types.

The Benefits

- High target specificity and increased safety
- High *in vivo* stability
- Easy to make
- Ease of delivery – can be injected w/o carriers

The Package

- The agent has been tested *in vitro* and *in vivo* and a solid data package is available.
The Problem with Small Molecule Therapeutics in Cancer Therapy

- Toxicity and undesired side effects from off-target activity and injuring of normal cells.
- No effective treatment for metastasis.
- For glioma traditional small-molecule therapeutics need to cross the blood-brain-barrier.
- Small molecule therapeutics often require costly synthetic processes.
- Delivery requires optimized formulation.
- Problems with metabolic stability.
Matrix metalloproteinase expression is correlated with tumor invasion and metastasis.

Blocking matrix metalloproteinase (MMP-9) expression with a DNAzyme is able to inhibit tumor growth.

The Difference: Unlike traditional small molecules, which inhibit matrix metalloproteinases by binding to the active site of the protein, catalytic DNAzymes work by degrading the mRNA and blocking the protein from being produced.
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<th><strong>DNAzyme</strong></th>
<th><strong>Traditional MMP Inhibitors</strong></th>
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<tr>
<td>• Prevents MMP–9 from being produced</td>
<td>• Block active site of MMP</td>
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<td>• Specific only for MMP–9 w/o affecting other MMP</td>
<td>• Affect other members of the MMP family as well</td>
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<td>• Easy production</td>
<td>• Involves multi-step synthetic processes</td>
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<td>• Injected naked</td>
<td>• Requires optimized formulation and delivery</td>
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Block of mRNA Expression by Degrading the RNA:

- mRNA
- DNAzyme
- $M^+$
- cleaved mRNA
- DNAzyme
The DNAzyme exhibits high in-vivo efficacy in a Rat model:

Weekly intracranial treatment of rats bearing glioma with 40 µg or 100 µg AM9D DNAzyme reduced mean tumor burden by 50% or 75% respectively.

**Tumor reduction** in rats bearing brain tumors after treatment with 40µg or 100µg DNAzyme per tumor, compared to control groups.

Fluorescence imaging of the tumor in the brain of mice before (A) and after (C) treatment with the DNAzyme. Dissected brain of an untreated mouse (B) compared to a mouse treated with the DNAzyme (D). The tumor appears purple.
The DNAzyme Triggers Angiogenesis and Apoptosis in Cancer Cells

**Angiogenesis**: The AM9D DNAzyme reduces the formation of new blood vessels in cancer cells which leads to **tumor reduction and cancer cell death**.

**Apoptosis**: Treatment with AM9D DNAzyme initiates the apoptotic process that leads to **cancer cell death**.
The Stability of DNAzyme AM9D is demonstrated with fluorescently-labeled AM9D injected into mammary tumors and resected at either (a) 7 days, (b) 10 days, or (c) 14 days post-injection.

After 14 days the DNAzyme is still alive and well.
Distribution and Clearance Profile

**Distribution**
- The DNAzyme distributes well to all tissues, including the brain, which makes it a suitable candidate for brain cancer.

**Clearance**
- The DNAzyme eliminates from all tissue.
- 43% clear from the system over 72 hours.
The Inventor

Dr. Tayebeh Pourmotabbed is a Professor of Molecular Sciences in the College of Medicine at the University of Tennessee Health Science Center. Her research interests include cancer therapy, understanding the structure–function relationship of matrix metalloproteinases, and identifying risk factors in Alzheimer’s and coronary artery disease. She can be reached at tpourmot@uthsc.edu